Applicant regards as the invention. Amendment of claim 27 to delete the recitation "and" at the end of the claim renders the Examiner's rejection moot with respect to these claims.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 29-31 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that "one skilled in the art would have reason to doubt an unsupported assertion that conventional methods such as intramuscular injection would supply both plasmid DNA and MVA virus to enough of the same cells, to express enough of the antigen, to produce the desired immune response in vivo." (Office Action, page 3). Applicant traverses the rejection for the reasons presented below.

The first paragraph of 35 U.S.C. § 112 requires that the claimed invention be adequately described so as to enable the skilled artisan to make and use the invention. The specification teaches how to administer the composition comprising two components, specifically a vector (e.g., a plasmid) expressing more than one Dengue virus serotype antigen under the transcriptional control of a T7 RNA polymerase promoter and a recombinant MVA virus expressing T7 RNA polymerase.(e.g., page 5, lines 19-27, page 7, lines 5-6; page 10, lines 13-28) and methods of administration of the two component composition to an animal (e.g., page 10, lines 13-28, page 20, lines 6-15). The specification teaches the timing of administration of the two components to optimize co-expression of the antigen in cells (e.g., page 10, lines 13-28) and *how to optimize coexpression of the two components by using the same inoculation site for*

both components (e.g., page 7, lines 3-8). Thus, contrary to the Examiner's allegations, the specification does teach the skilled artisan how to make and use the instantly claimed invention. Applicant need not exemplify every possible claimed embodiment [In re Robins 429 F.2d 456,456-457, 166 U.S.P.Q. 556, 555 (CCPA 1970)] or provide working examples [In re Strahilevitz 668 F 2d 1229, 212 U.S.P.Q. 561 (CCPA, 1982)] to satisfy the first paragraph of 35 U.S.C. § 112.

Moreover, enablement is determined from the viewpoint of the skilled artisan using the knowledge and skill with which such a person is charged. Northern Telecom, Inc. v Datapoint Corp., 908 F 2d 931, 15 U.S.P.Q 2d 1321 (Fed. Cir. 1990); Lindemann Maschinenfabrik v. American Hoist & Derrick Co. 730 F 2d 1452,221 USPQ 481 (Fed. Cir 1984). At the time of filing of the instant application, the properties of the MVA virus had been demonstrated in clinical trials (page 5, lines 1-18), MVA vaccines had been used for vaccination against smallpox (page 19, lines 28-34) and an MVA virus expressing T7 polymerase was also known in the art (page 18, lines 19-35, page 19, lines 1-20). In addition, as noted by the Examiner, cells are easily co-transformed or transfected simultaneously or sequentially with the T7 promoter/vaccinia combination (Office action, page 3). Thus, the state of the art at the time of filing the instant application was such that a skilled artisan would have been readily able know how to make and use a vector expressing more than one dengue virus antigens in conjunction with an MVA virus expressing a T7 polymerase to mount an immune response in an animal.

In fact, the instant specification specifically addresses how to supply both components of the vaccine to a sufficient number of cells to produce the desired immune

response. The specification teaches that the MVA encoding T7 RNA polymerase may be inoculated (e.g., intramuscular injection) after (e.g., with a time lag) the vector expressing the dengue virus antigens under the control of T7 RNA polymerase promoter (page 10, lines 13-28). A time lag allows the cell to take up the vector expressing the dengue virus antigens before MVA infection takes place. The specification teaches administration (e.g., inoculation) of both components at the same site since nearly all cells close to the injection site will contain the vector encoding the dengue epitopes, resulting in cells recombinant for both components. Thus, most of the cells close to the application site will express the dengue antigens.

Alternatively, at the time of filing of the instant application an *ex vivo* vaccination approach was also known to those skilled in the art. Cells from the animal in need of treatment are isolated, then both vectors are introduced into said cells by transfection and/or infection *in vitro* and the transformed cells are reintroduced into the animal and an immune response produced. As noted by the Examiner, this method of cotransfection or coinfection *in vitro* is easily performed. (Office Action, page3).

In making a rejection under 35 U.S.C. § 112, the Examiner should provide evidence that the specification fails to teach one skilled in the art to make and use the claimed invention without undue experimentation. See In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1980). Applicant submits that the specification enables one of skill in the art to practice the invention without undue experimentation. To one of skill in the art, once the proper combination of vectors and antigen is identified (e.g., a vector expressing more than one Dengue virus serotype antigen under the control of a T7 RNA polymerase promoter and a recombinant MVA virus

expressing T7 RNA amino acid sequence), it is a matter of routine experimentation to proceed with administration. While optimization for the administration of a vector expressing more than one Dengue virus serotype antigen under the control of a T7 RNA polymerase promoter and a recombinant MVA virus expressing T7 RNA polymerase may be required, this optimization is a routine matter and well within skill in the art. Even if the optimization is potentially labor intensive, for one of skill in the art it would not constitute undue experimentation. The Federal Circuit has explicitly held that See id. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. (citing In re Angstadt, 537 Fd.2d 489, 502-04 (CPA 1976). Accordingly, Applicant respectfully submits that any experimentation required to practice Applicants invention is not undue, but rather routine for those skilled in the art.

The Examiner's assertion that one skilled in the art would have "reason to doubt that conventional methods such as intramuscular injection would supply both plasmid DNA and MVA virus to enough of the same cells, to express enough of the antigen, to produce the desired immune response in vivo" without undue experimentation is based on mere speculation. The Patent Office has a burden to "set forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes of course, providing any reasons for doubting any assertions on the specification as to the scope of enablement." In re Wright, 999 F2d 1557, 1562, 27 USPQ 2d 1510, 1522 (Fed. Cir. 1993). Accordingly, Applicant

respectfully submits that the Examiner has not met his burden of providing reasons or evidentiary support for the alleged non-enablement of the instant disclosure. In re Marzocchi 439 F.2d 220; 169 U.S.P.Q. 367 (CFCA 1971). Accordingly, based on the foregoing arguments, Applicant respectfully requests withdrawal of this ground of rejection.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 15-17, and 19-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Sutter et al (C2) or Altenburger (US 5,185,146), in view of Lai et al (US 5,494,671), and further in view of either Monath et al (Fields Virology) or Kelly et al (US 6,074,865), and any of Moss or Paoletti et al (WO 92/15672) or Nazerian et al (US 5,369,025). Applicant traverses this ground of rejection for the reasons discussed below.

Sutter et al relates to the use of a recombinant vaccinia vector system as an expression vector. Likewise, Altenburger et al relates to the use of MVA as an expression system. The instantly claimed invention is based on a discovery by the Applicant that vaccination with a recombinant MVA virus expressing more than one Dengue virus serotype antigen (e.g., at least one antigen from two or more virus serotypes) results in immunity against all four serotypes of Dengue virus. Sutter et al and Altenburger et al generally relate to the use of expression vectors based on vaccinia virus. However, neither Sutter et al or Altenburger et al teach or suggest the use of these vector systems to express more than one Dengue virus serotype antigen or the use of such systems to provide immunity against all four Dengue virus serotypes. Thus, Sutter et al or Altenburger et al cannot render the claimed invention obvious.

Lai et al describes a vaccinia virus expressing only a serotype 4 dengue antigen which is suitable to induce an immune response only against dengue virus serotype 4. As discussed in Applicant's earlier response, immunization of a subject against one dengue virus subtype may result in antibody-dependent enhancement and/ or immune enhancement, when the subject is later infected with a different dengue virus serotype. The long standing problem was to find a vaccine against dengue virus infection, which does not provoke antibody-dependent enhancement and/ or immune enhancement. Lai et al does not teach or suggest a solution to this problem. The solution is found only in Applicant's claimed invention. In fact, prior to Applicant's invention, the skilled artisan would have believed that infection with two or more Dengue virus serotypes would result in severe side effects.Thus, the prior art actually taught away from Applicant's claimed invention. Accordingly, Lai et al does render the claimed invention obvious either alone or in combination.

Monath et al (page 1002, column 2) relates to vaccination with live, attenuated dengue viruses of all four serotypes in order to avoid immune enhancement or antibody dependent enhancement. In Monath complete dengue viruses of the different serotypes are used for vaccination. Consequently, a high number of different antibodies, each directed against a different antigen, is provoked by the vaccine. The assumption being that the diversity of antibodies provoked in the subject will allow protection against all dengue virus serotypes. Thus, Monath et al solves the problem of immune enhancement and/or antibody dependent enhancement by using the complete dengue virus genomes (i.e., a multitude of different antigens). In contrast, the instant invention uses MVA as a vector for specific antigens (e.g., pre-

M,E, NS-1) of the four dengue virus serotypes. Based on Monath, the skilled practitioner would not expect that specific isolated antigens of one or more dengue virus serotypes would be effective as a vaccine. As discussed above, the skilled artisan would likely believe that such a vaccine would provoke immune enhancement or antibody dependent enhancement. In fact, Monath et al, notes that induction of immune enhancement or antibody dependent enhancement is a serious concern for the use of subunit vaccines (page 1003, column 1, last paragraph). Accordingly, Monath et al, either alone or in combination, does not render the claimed invention obvious.

Kelly et al relates to the to a recombinant fragment of dengue virus serotype 2 expressed in a baculovirus. Kelly et al does not teach or suggest that at least one antigen from two or more virus serotypes results in immunity against all four serotypes of Dengue virus. Thus, Kelly et al does not render the deficiences of the prior references and cannot render the claimed invention obvious.

Moss is a general reference relating to the use of recombinant DNA virus vectors for vaccination. Moss does not teach or suggest a recombinant MVA virus expressing more than one Dengue virus serotype antigen results in immunity against all four serotypes of Dengue virus. Likewise, Paoletti et al relates to the expression of three serotypes of *avian influenza virus* in a fowlpox virus. Paoletti et al also does not teach or suggest a recombinant MVA virus expressing more than one Dengue virus serotype antigen. Further, neither Moss or Paoletti teach or suggest that a vaccine that solves the problem of immune enhancement and/or antibody dependent enhancement associated with Dengue virus vaccination. Such a disclosure is found

only in the instant application. Accordingly, neither Moss or Paoletti et al, either alone or in combination render the claimed invention obvious.

Nazarian et al relates to a fowlpox virus recombinant for a sequence encoding the glycoprotein B homologue (gBh) of Marek's disease virus (MDV). This, Nazarian does not remedy the deficiencies of either Moss or Paoletti or any of the references cited by the Examiner. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Sutter et al (C2) or Altenburger (US 5,185,146), in view of Lai et al (US 5,494,671), and either Monath et al (Fields Virology) or Kelly et al (US 6,074,865), and any of Moss or Paoletti et al (WO 92/15672) or Nazerian et al (US 5,369,025), as applied to claims 15-17 and 19-26 above, and further in view of further in view of Sutter et al (PNAS 89:10847-1085 1, 1992), for essentially the same reasons as the previous rejection of claim 4. Applicant traverses this rejection for the reasons provided below.

As discussed above, neither Sutter et al (C2) or Altenburge, Lai et al, Monath et al or Kelly et al, Moss or Paoletti et al or Nazerian et al render the claimed invention obvious. Sutter et al (PNAS) relates to the use of recombinant MVA virus as a vector for heterologous gene expression. Sutter et al (PNAS) does not teach or suggest the use of a recombinant MVA virus to express more than one Dengue virus serotype antigen, or that such a construct may be used as a vaccine to provide immunity against all four Dengue virus serotypes. Accordingly, Sutter et al does not remedy the deficiency of Sutter et al (C2), Altenburge, Lai et al, Monath et al, Kelly et al, Moss, Paoletti et al or Nazerian. Accordingly, Sutter et al, either alone or in

combination cannot render the claimed invention obvious. Withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims comply with 35 U.S.C. § 112, first and second paragraph and define an invention that is patentable over the art. Accordingly, allowance is in order, and an early notification to that effect would be appreciated. Should the Examiner in reviewing the communication have any questions or need any additional information, she is welcome to contact the undersigned at (650) 849-4902.

The Assistant Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 50-1189. Docket No.: 20239-703. A DUPLICATE COPY OF THIS SHEET IS ATTACHED.

Respectfully submitted,

Dated: September 10, 2001

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Exhibit A

Version of the Amendments to the Claims with Markings to Show Changes Made

27. (Amended) A composition comprising a first and second component, wherein the first component is a vector comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 antigen, a DNA sequence encoding a Dengue virus serotype 2 antigen, a DNA sequence encoding a Dengue virus serotype 3 antigen, or a DNA sequence encoding a Dengue virus serotype 4 antigen and wherein the more than one DNA sequences are under the transcriptional control of a T7 RNA polymerase promoter and the second component is a recombinant Modified Vaccinia Ankara (MVA) virus comprising a DNA sequence encoding T7 RNA polymerase [and].

32. (New) A cell containing the composition of claim 27.

33. (New) A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 preM antigen, a DNA sequence encoding a Dengue virus serotype 2 preM antigen, a DNA sequence encoding a Dengue virus serotype 3 preM antigen, and a DNA sequence encoding a Dengue virus serotype 4 preM antigen.

34. (New) The recombinant Modified Vaccinia Ankara (MVA) virus of Claim 33 comprising a DNA sequence encoding a Dengue virus serotype 1 preM antigen, a DNA sequence encoding a Dengue virus serotype 2 preM antigen, a DNA sequence encoding a Dengue virus serotype 3 preM antigen, and a DNA sequence encoding a Dengue virus serotype 4 preM antigen.

35. (New) A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 E antigen, a DNA sequence encoding a Dengue virus serotype 2 E antigen, a DNA sequence encoding a Dengue virus serotype 3 E antigen, and a DNA sequence encoding a Dengue virus serotype 4 E antigen.

36. (New) The recombinant Modified Vaccinia Ankara (MVA) virus of Claim 35 comprising

a DNA sequence encoding a Dengue virus serotype 1 E antigen, a DNA sequence encoding a Dengue virus serotype 2 E antigen, a DNA sequence encoding a Dengue virus serotype 3 E antigen, and a DNA sequence encoding a Dengue virus serotype 4 E antigen.

37. (New) A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 2 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 3 NS-1 antigen, and a DNA sequence encoding a Dengue virus serotype NS-1 antigen.

38. (New) The recombinant Modified Vaccinia Ankara (MVA) virus of Claim 37 comprising a DNA sequence encoding a Dengue virus serotype 1 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 2 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 3 NS-1 antigen, and a DNA sequence encoding a Dengue virus serotype NS-1 antigen.

Exhibit B

Currently Pending Claims

15. A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 antigen, a DNA sequence encoding a Dengue virus serotype 2 antigen, a DNA sequence encoding a Dengue virus serotype 3 antigen, and a DNA sequence encoding a Dengue virus serotype 4 antigen.

16. The recombinant MVA virus according to Claim 15, wherein the recombinant MVA virus comprises a DNA sequence encoding a Dengue virus serotype 1 antigen, a DNA sequence encoding a Dengue virus serotype 2 antigen, a DNA sequence encoding a Dengue virus serotype 3 antigen, and a DNA sequence encoding a Dengue virus serotype 4 antigen.

17. The recombinant MVA virus according to Claim 15, wherein the Dengue virus antigen is selected from the group consisting of preM, E and NS1 antigens.

18. The recombinant MVA virus according to Claim 15, wherein the DNA sequences are is inserted at the site of one or more naturally occurring deletions within the MVA virus genome.

19. The recombinant MVA virus according to Claim 15, wherein the DNA sequences encoding antigens are under transcriptional control of the vaccinia virus early/late promoter P7.5.

20. A pharmaceutical composition comprising at least one recombinant MVA virus according to Claim 15 and a pharmaceutically acceptable carrier or diluent.

21. A pharmaceutical composition comprising at least one recombinant MVA virus according to Claim 16 and a pharmaceutically acceptable carrier or diluent.

22. A pharmaceutical composition comprising at least one recombinant MVA virus according to Claim 19 and a pharmaceutically acceptable carrier or diluent.

23. A method for mounting an immune response in an animal to Dengue virus infection, the method comprising administering to the animal the pharmaceutical composition of Claim 20.

24. The method according to Claim 23, wherein the animal is a human.

25. A method for mounting an immune response in an animal to Dengue virus infection, the method comprising administering to the animal the pharmaceutical composition of Claim 21.

26. The method according to Claim 25, wherein the animal is a human.

27. A composition comprising a first and second component, wherein the first component is a vector comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 antigen, a DNA sequence encoding a Dengue virus serotype 2 antigen, a DNA sequence encoding a Dengue virus serotype 3 antigen, or a DNA sequence encoding a Dengue virus serotype 4 antigen and wherein the more than one DNA sequences are under the transcriptional control of a T7 RNA polymerase promoter and the second component is a recombinant Modified Vaccinia Ankara (MVA) virus comprising a DNA sequence encoding T7 RNA polymerase.

28. The composition of Claim 27, wherein the vector of the first component is a plasmid.

29. A method for mounting an immune response in an animal to Dengue virus infection, the method comprising administering to the animal the composition of Claim 27.

30. The method according to Claim 29, wherein the animal is a human.

31. The method of Claim 29 wherein the first component is administered prior to the second component.

32. A cell containing the composition of claim 27.

33. (New) A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 preM antigen , a DNA sequence encoding a Dengue virus serotype 2 preM antigen, a DNA sequence encoding a Dengue virus serotype 3 preM antigen, and a DNA sequence encoding a Dengue virus serotype 4 preM antigen.

34. (New) The recombinant Modified Vaccinia Ankara (MVA) virus of Claim 33 comprising a DNA sequence encoding a Dengue virus serotype 1 preM antigen, a DNA sequence encoding a Dengue virus serotype 2 preM antigen, a DNA sequence encoding a Dengue virus serotype 3 preM antigen, and a DNA sequence encoding a Dengue virus serotype 4 preM antigen.

35. (New) A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 E antigen, a DNA sequence encoding a Dengue virus serotype 2 E antigen, a DNA sequence encoding a Dengue virus serotype 3 E antigen, and a DNA sequence encoding a Dengue virus serotype 4 E antigen.

36. (New) The recombinant Modified Vaccinia Ankara (MVA) virus of Claim 35 comprising a DNA sequence encoding a Dengue virus serotype 1 E antigen, a DNA sequence encoding a Dengue virus serotype 2 E antigen, a DNA sequence encoding a Dengue virus serotype 3 E antigen, and a DNA sequence encoding a Dengue virus serotype 4 E antigen.

37. (New) A recombinant Modified Vaccinia Ankara (MVA) virus comprising more than one DNA sequence selected from the group consisting of a DNA sequence encoding a Dengue virus serotype 1 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 2 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 3 NS-1 antigen, and a DNA sequence encoding a Dengue virus serotype NS-1 antigen.

38. (New) The recombinant Modified Vaccinia Ankara (MVA) virus of Claim 37 comprising a DNA sequence encoding a Dengue virus serotype 1 NS-1 antigen, a DNA sequence encoding a Dengue virus serotype 2 NS-1 antigen, a DNA sequence encoding a

Dengue virus serotype 3 NS-1 antigen, and a DNA sequence encoding a Dengue virus serotype NS-1 antigen.